present invention include "autoimmune disorders in which the reaction to self primarily involves cell-mediated immune mechanisms, as opposed to humoral immune mechanisms;" and "the methods of the present invention pertain to treatments of autoimmune disorders in which tissue destruction is primarily mediated through activated T cells and immune cells other than B lymphocytes."

Patentability Remarks

35 U.S.C. §102(e)

Claims 1 and 4-10 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,683,693 of Noelle et al. ("the '693 patent") for the reasons of record stated in Paper No. 9. As amended, the claims of the present application are directed to a method consisting essentially of administering a gp39 antagonist to inhibit or prevent T cell-mediated tissue destruction resulting from cell-mediated autoimmune reactions associated with type I diabetes. The '693 patent of Noelle et al. describes a method for inducing tolerance to transplanted allogeneic or xenogeneic cells comprising administering (a) an allogeneic or xenogeneic cell, and (b) a gp39 antagonist; but it does not describe a method for inhibiting or preventing T cell-mediated tissue destruction associated with type I diabetes consisting essentially of administering a therapeutically or prophylactically effective amount of gp39 antagonist; for example, to inhibit cell-mediated tissue destroying immune reactions in an autoimmune disease, as in the present invention. Withdrawal of the rejection is respectfully requested.

Claims 1 and 4-10 were also rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,993,816 of Lederman et al. ("the '816 patent") for the reasons of record stated in Paper No. 9. The examiner points to lines 27-35 of column 11 of the '816 patent, which states that the invention disclosed in the patent is valuable as a method of inhibiting the autoimmune response in an animal suffering from an autoimmune disease such as diabetes mellitis.

The rejection of the claims in view of the '816 patent is respectfully traversed. One skilled in the art would have understood the statement in the '816 patent regarding the value of administering a gp39 antagonist to inhibit an autoimmune response associated with an autoimmune disease in the context of the patent as a whole, which teaches that the gp39

antagonist exerts its therapeutic effect by inhibiting a humoral immune response by preventing the activation of B cells by T cells. For example, at column 6, lines 52-56:

> "This invention provides a monoclonal antibody which specifically recognizes and forms a complex with a protein located on the surface of activated T cells thereby inhibiting T cell activation of B cells.

At column 9, lines 21-23:

> "This invention provides an isolated protein from the surface of activated T cells that is necessary for T cell activation of B cells;"

At column 9, line 66, to column 10, line 1:

> "This invention provides an isolated, soluble protein from the surface of activated T cells necessary for T cell activation of B cells."

And at column 10, lines 60-61:

> "This invention provides a method of inhibiting B cell activation in an animal ..."

Furthermore, persons of ordinary skill in the art would reasonably understand the paragraph in column 11 (lines 27-35) of the '816 patent that describes using the disclosed method to inhibit the autoimmune response in an animal suffering from autoimmune disease, in view of the description of the disclosed invention in the two preceding paragraphs at column 11, lines 17-26, as shown below:

> " The method of inhibiting B cell activation is valuable in a new and useful method for inhibiting the immune response of an animal. In one embodiment of this invention, the animal is a mammal, for example a mouse or a human. preferably, the mammal is a human.
>
> In one embodiment of this invention, inhibiting the immune response of an animal is valuable as a method of inhibiting the rejection by the animal of a transplant organ, for example, a heart, kidney or liver.
>
> In another embodiment of this invention, inhibiting the immune response of an animal is valuable as a method of inhibiting the autoimmune response in an animal suffering from autoimmune disease. Examples of autoimmune diseases include, but are not limited to, rheumatoid arthritis, Myasthenia gravis, systemeic lupus erythematosus, Graves' disease, idiopathic thrombocytopenia purpura, hemolytic anemia, diabetes mellitus and drug-induced autoimmune diseases, e.g., drug-induced lupus."

All of the descriptions of the biological activity of antibody 5c8 provided in the '816 patent relate to inhibiting a humoral immune response by inhibiting the activation of B cells by T cells; therefore, a person of ordinary skill in the art would reasonably have concluded that the method for inhibiting an autoimmune response in an animal suffering from autoimmune disease described in column 11 of the '816 patent is useful for inhibiting the pathological effects of an autoimmune disease that are the result of a humoral autoimmune response; *i.e.*, one that is mediated by antibodies produced by B cells. In contrast, the present application describes the claimed invention as a method for inhibiting T cell mediated tissue destruction resulting from a cell-mediated immune reaction to a self-antigen. (page 3, bottom paragraph, emphasis added). The term "cell-mediated" that is used to describe the tissue-destroying autoimmune reactions treated by the claimed invention is intended in the present application to refer to the set of immune reactions that are "primarily mediated through activated T cells and immune cells other than B lymphocytes" (page 3, lines 33-36, emphasis added). At the time the invention was made, tissue-destroying cell-mediated immune reactions, which include induction of target cell death through direct cellular contact and through release of soluble cytotoxins, were known by those skilled in the art to be distinct from humoral, antibody-mediated immune reactions, both in the types and timing of the tissue damage caused by the two types of immune reactions. See the description of cellular and humoral immune systems in "The Biology of the Immune System," § 2(2), The Merck Manual of Diagnosis and Therapy, 13th Edition, R. Berkow, editor, Merck, Sharp & Dohme Research Laboratories, Rahway, NJ, 1977, pages 195-197 (copy attached). As discussed in the applicants' previous reply, Casares et al. (Curr Mol. Med., 2001, 1(3):357-378, copy attached) described T cell-mediated, cellular immune responses that occur in the initiation of Type 1 diabetes that result in the destruction of pancreatic islet beta cells; e.g., through islet infiltration and direct T cell-beta cell contact, or through release of soluble mediators that elicit beta cell destruction, without the involvement of a B cell-mediated humoral, or antibody-dependent immune response (see pp. 362-363). The timing and pathology of T cell-mediated, tissue-destroying cellular autoimmune responses associated with Type 1 diabetes are distinctly different from the humoral component of the disease. The '816 patent neither describes nor suggests the claimed method for inhibiting or preventing tissue destruction associated with type I diabetes consisting of administering a therapeutically or prophylactically effective amount of a gp39 antagonist, in the case where the tissue

destruction results from a cell-mediated immune reaction to a self-antigen. The applicants observe that the examiner has previously recognized a method for inhibiting transplant rejection comprising administering a gp39 antagonist to induce T cell non-responsiveness as being distinct from the teaching of the '816 patent to administer a gp39 antagonist to inhibit B cell activation by T cells in association with transplant rejection. See the Interview Summary dated 10/28/97 and the Examiner's Reasons for Allowance in the Notice of Allowability dated 9/28/98 of U.S. Application No. 08/906,332, now U.S. Patent No. 5,902,585 (copies attached). The applicants recognize that each application must be considered on its own merits. However, applicants submit that the distinctions between the induction of T cell non-responsiveness and the inhibition of B cell activation by T cells in transplant rejection that distinguished the method of U.S. Patent No. 5,902,585 from the '816 patent are comparable to the distinctions between the inhibition of T cell mediated, tissue-destroying cellular immune reactions and the inhibition of B cell activation by T cells in treating an autoimmune disease that are at issue in the rejection of the present claims over the '816 patent.

Claims 12-20 are directed to a method that uses antibodies that are expressly described as having variable regions of antibody 24-31 or 89-76, which are specific, chemical entities that are not described or disclosed by the '816 patent.

In view of the foregoing, the applicants respectfully submit that the present claims, amended as shown above, are not anticipated by Lederman et al., and withdrawal of the rejection is requested.

35 U.S.C. §103(a)

Claims 1, 4-10, and 12-20 were rejected under 35 U.S.C. 103(a) over the '693 patent of Noelle et al., alone or in combination with the '816 patent of Lederman et al., together with U.S. Patent No. 5,747,037 of Noelle et al. ("the '037 patent"), also for the reasons of record stated in Paper No. 9. The '037 patent is described in the office action (p. 4) as disclosing the 24-31 and 89-76 antibodies and "their use as therapeutic antagonists in inhibiting various immune responses."

As discussed above, the '693 patent describes a method for inducing T cell tolerance (or non-responsiveness) to an antigen comprising administering both a gp39 antagonist and a cell that presents to a T cell the antigen against which tolerance is to be induced. For

example, see col. 8, line 57, to col. 9, line 8. However, the '693 patent does not describe the claimed method for inhibiting or preventing T cell-dependent, cell-mediated tissue destroying immune reactions associated with type I diabetes consisting essentially of administering a therapeutically or prophylactically effective amount of gp39 antagonist. The '037 patent similarly describes a method for inducing T cell tolerance or non-responsiveness to an antigen comprising administering both a gp39 antagonist and a cell that presents to a T cell the antigen against which tolerance is to be induced. See col. 9, line 54, to col. 11, line 22. Like the '693 patent, the '037 patent does not describe a method for inhibiting or preventing T cell-dependent, cell-mediated tissue destroying immune reactions associated with type I diabetes consisting essentially of administering a therapeutically or prophylactically effective amount of gp39 antagonist. The '037 patent therefore does not provide the teachings missing from the '693 patent that are necessary to establish *prima facie* obviousness of the claimed invention.

The '816 patent describes a method for inhibiting activation of B cells by T cells in an autoimmune disease such as diabetes comprising administering a gp39 antagonist; but it does not describe or suggest a method in which a gp39 antagonist is administered to inhibit or prevent T cell-dependent tissue destruction associated with type I diabetes that results from a cell-mediated immune reaction to a self-antigen. At the time the invention was made, the teachings of the '816 patent regarding the use of a gp39 antagonist to inhibit B cell activation would not have suggested to one of ordinary skill in the art that a gp39 antagonist could be administered to a subject to successfully inhibit or prevent tissue destruction associated with type I diabetes that results from a cell-mediated immune reaction to a self-antigen. Again, '037 patent does not provide the additional teachings required to establish that the claimed invention would have been obvious to one of ordinary skill in the art. Withdrawal of the rejection of the claimed invention under 35 U.S.C. 103(a) is therefore respectfully requested.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal

or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP, LLP

By _____

Thomas A. Cawley, Jr., Ph.D.
Reg. No.: 40944
Tel. No.: (703) 905-2144
Fax No.: (703) 905-2500

PILLSBURY WINTHROP LLP
P.O. Box 10500
McLean, VA 22102

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/475873 — 1427/2-34

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/906332			

305-7939

OIPE OCT 09 2003 PATENT & TRADEMARK OFFICE JC46

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) ROBIN TESKIN (3) PHILLIP GAMBEL

(2) RANDOLPH NOELLE (4)

Date of Interview 10/28/97

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☑ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No If yes, brief description:

Agreement ☑ was reached. ☐ was not reached.

Claim(s) discussed: PENDING/PROPOSED

Identification of prior art discussed: OF RECORD

ER. INDICATED ANTAGONISTS SHOULD BE $\alpha_4\beta_7$ ABS AND SOLUBLE $\alpha_4\beta_7$

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:

APPLICNT/EXAM. DISCUSSED PROPOSED CLMS AND HOW INHIBITING GRAFT REJECTION IS NOT MET BY PRIOR ART PARTICULARLY IN VIEW OF LEDERMAN REFS; ANDREO, NOELLE - EXAM INDICATED THAT PRIOR ART DID NOT PROVIDE GUIDANCE FOR T-CELL MEDIATED GRAFT REJECTION; EXAM. WILL RE-EVALUATE AFTER FINAL AMD.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☑ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

FORM PTOL-413 (REV.1-96)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

OP/9063332

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/906,332	08/05/97	NOELLE R	01271-423

HM11/0928

E JOSEPH GESS
BURNS DOANE SWECKER & MATHIS
P O BOX 1404
ALEXANDRIA VA 22313-1404

EXAMINER	
GAMBE	

ART UNIT	PAPER NUMBER
1644	28

DATE MAILED: 09/28/98

NOTICE OF ALLOWABILITY

PART I.

1. ☐ This communication is responsive to 8/5/97, 10/17/97, 11/3/97, 7/9/98, 9/11/98.
2. ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☐ The allowed claims are 48, 54-55, 57-68, 70-79, 91-94, 96-100 (renumbered 1-34).
4. ☐ The drawings filed on 8/5/97 are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [_] not been received. [X] been filed in parent application Serial No. _____, filed on _____.
6. ☐ Note the attached Examiner's Amendment.
7. ☐ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☐ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☐ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- _ Examiner's Amendment
- _ Examiner Interview Summary Record, PTOL-413
- _ Reasons for Allowance
- _ Notice of References Cited, PTO-892
- _ Information Disclosure Citation, PTO-1449
- _ Notice of Informal Application, PTO-152
- _ Notice re Patent Drawings, PTO-948
- _ Listing of Bonded Draftsmen
- _ Other

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1644, Group 1640, Technology Center 1600.

2. Applicant's amendment, filed 8/5/97 (Paper No. 2) is acknowledged.
Claims 2-51 have been canceled.

Applicant's amendment, filed 10/27/97 (Paper No. 3) is acknowledged.
Claim 1 has been canceled
Claims 52-100 have been added.

Applicant's amendment, filed 11/3/97 (Paper No. 4) is acknowledged.
Claims 56, 83 and 95 have been canceled
Claims 52, 60, 65, 72-74, 86, 87 , 92 and 99 have been amended.

EXAMINER'S AMENDMENT

3. An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

4. Authorization for this Examiner's Amendment was given in a telephone interview with Robin Teskin on 9/22/98.

5. Replace the title with the following:
-- METHODS OF INDUCING T CELL UNRESPONSIVENESS TO DONOR TISSUE OR ORGAN IN A RECIPIENT WITH GP39 ANTAGONISTS -- .

6. Amend the first line of the specification, by adding after "application No. 08/234,987, filed April 25, 1994" : --, now U.S. Patent No. 5,683,693 -- .

7. Amend claim 52, line 4, by replacing "exposed to" with -- transplanted with -- .

8. Amend claim 52, line 10, by adding after "fragments thereof" with
--that specifically bind gp39 -- .

9. Amend claim 57, line 2, by adding after "chimeric monoclonal antibody"
-- wherein said chimeric monoclonal antibody comprises a non-human animal variable region and a human constant region -- .

10. Amend claim 65, line 4, by replacing "exposed to" with -- transplanted with -- .

11. Amend claim 65, line 7, by adding after "fragments thereof" with
-- that specifically bind gp39 -- .

12. Cancel claim 69.

13. Amend claim 70, line 2, by adding after "chimeric monoclonal antibody" -- wherein said chimeric monoclonal antibody comprises a non-human animal variable region and a human constant region -- .

14. Amend claim 75, by replacing "claim 64" with claim -- 74 -- .

15. Amend claim 75, by replacing the "lymphoid" cell with -- allogeneic or xenogeneic -- cell.

16. Cancel claims 80-91.

17. Amend claim 92, line 4, by replacing "exposed to" with -- transplanted with -- .

18. Amend claim 92, line 5, by adding after "fragment thereof" with --that specifically binds gp39 -- .

19. Amend claim 96, line 2, by adding after "chimeric monoclonal antibody" -- wherein said chimeric monoclonal antibody comprises a non-human animal variable region and a human constant region -- .

REASONS FOR ALLOWANCE

20. The following is an Examiner's Statement of Reasons for Allowance:

Upon reconsideration of the prosecution in parent application USSN 08/234,987, now U.S. Patent No. 5,683,693, and addressed in an interview on 11/28/97 in conjunction with the instant claims; the instant methods of inducing T cell non-responsiveness to donor tissues or organs in recipients with gp39(CD40 ligand) antagonists were unobvious at the time the invention was made. Accordingly the claims of this application are deemed allowable

It is noted that the recitation of "administering to a recipient which has or is to become transplanted with" is drawn to the administration of cells prior to or simultaneously/contemporaneously with gp39 antagonists as set forth on page 10, paragraph 1 of the instant specification.

The terminal disclaimers filed on 7/9/98 (Paper No. 6), disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of USSNs 08/232,0929; 08/234,987 (now U.S. Patent No. 5,683,693); and 08/727,486 have been reviewed and is accepted. The terminal disclaimers have been recorded.

OTHER ISSUES

21. The application is required to be reviewed and all spelling and like errors corrected. Applicant is reminded that BALB/c" is the proper designation of this mouse strain.

22. Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee and, to avoid processing delays, should preferably **accompany** the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Patent Examiner
Group 1640
Technology Center 1600
September 22, 1998

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1600